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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/785,632	02/16/2001	Jin-Soo Kim	12279-002001	3563

26161 7590 06/20/2005

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EXAMINER	
MCKELVEY, TERRY ALAN	
ART UNIT	**PAPER NUMBER**
1636	

DATE MAILED: 06/20/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/785,632	KIM ET AL.	
	Examiner	Art Unit	
	Terry A. McKelvey	1636	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE *3* MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *04 April 2005*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-35,86-99,107,112 and 117-119* is/are pending in the application.

4a) Of the above claim(s) *24-31,34,35,87,94,99,107,112 and 117-119* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☐ Claim(s) *1-23,32,33,86,88-93 and 95-98* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/5/04, 11/12/03*, 7/23/03, 12/2/04
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

The text of those sections of Title 35, U.S. Code not included in this action can be found in a prior Office action.

All objections and rejections not repeated in the instant Action have been withdrawn due to applicant's response to the previous Action.

Election/Restrictions

Claims 24-31, 34-35, 87, 94, 99, 107, 112, and 117-119 are withdrawn from further consideration pursuant to 37 CFR 1.142(b), as being drawn to a nonelected invention and/or species, there being no allowable generic or linking claim. Applicant timely traversed the restriction (election) requirement in the reply filed on 9/9/02 and 10/30/03.

This application contains claims 24-31, 34-35, 87, 94, 99, 107, 112, and 117-119 drawn to an invention nonelected with traverse in a paper filed 9/9/02. A complete reply to the final rejection must include cancellation of nonelected claims or other appropriate action (37 CFR 1.144) See MPEP § 821.01.

Information Disclosure Statement

Upon review of the instant application, it was determined that although the IDS's of 1/5/04, 11/12/03, and 7/23/03 were previously considered, there is no record of sending the signed and initialed IDS forms to the applicant. This has been corrected with the instant action.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in

order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 1-11, 13-22, 32-33, 86, 88-93, and 95-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas, III et al (U.S. Patent No. 6,242,568 B1) in view of Cheng et al (U.S. Patent No. 5,869,250, Applicant reference EA). This is a new rejection necessitated by the applicant's amendment to the claims (removing the non-naturally occurring protein limitation) filed 4/4/05.

Barbas teaches a method for identifying a modulating polypeptide derived from a zinc-finger nucleotide binding polypeptide that binds to a zinc-finger-nucleotide binding motif of interest comprising incubating components, comprising a nucleotide sequence encoding the putative modulating protein (which comprises a trans-modulating protein sequence) operably linked to a first inducible promoter and a reporter gene operably linked to a second inducible promoter and a zinc-finger nucleotide binding motif, wherein the incubating is carried out under conditions sufficient to allow the components to interact, and measuring the effect of the putative modulating protein on the expression of the reporter gene, such as beta-galactosidase (columns 26-27). Incubation of the components may be in vitro

or in vivo, in vivo including prokaryotic or eukaryotic systems. Whether or not the putative modulating protein binds to the zinc finger-nucleotide binding motif which is operably linked the second inducible promoter, and affects its activity is measured by the expression of the reporter gene. Other commonly used assays to assess the function from a promoter, including CAT assay will be known to those of skill in the art. Both prokaryotic and eukaryotic systems can be utilized (column 27). The invention is useful for the identification of a novel zinc finger-nucleotide binding polypeptide derivative or variant and the nucleotide sequence encoding the polypeptide. The method entails modification of the fingers of a wild type zinc finger protein so that they recognize a nucleotide, either DNA or RNA, sequence other than the sequence originally recognized by that protein. In HIV, the target site for a zinc finger-nucleotide binding motif within the promoter is CTG-TTG-TGT. The three fingers of zif268, for example, are mutagenized, as described in the examples. The fingers are mutagenized independently on the same protein (one by one), or independently or "piecewise" on three different zif268 molecules and religated after being mutagenized (column 27). Zinc finger proteins of the invention can be manipulated to recognize and bind an extended target sequence, such as using from 2 to 20 zinc fingers (column 28).

Libraries of hybrid nucleic acids each of which encodes a polypeptide comprising a DNA binding region that recognizes part of the total zinc finger nucleotide binding motif (which reads on the claimed "recruitment site") and a randomized zinc finger, having conserved domain boundaries made by PCR from a template in cDNA, were made, the polypeptides expressed and assayed for binding to a modified binding site for each individual zinc finger using phagemid display/affinity selection (columns 34-45).

Barbas does not specifically teach use of the in vivo method of identifying a modulating polypeptide taught by the reference (using the reporter expression system), applied to identifying hybrid nucleic acids that encode a polypeptide comprising one test zinc finger domain (which potentially binds to a modified part of the zinc finger-nucleotide binding motif) and the two other zinc finger domains constant (binds to the unmodified part of the zinc finger-nucleotide binding motif). This reference also does not specifically teach the use of S. cerevisiae yeast cells for the assay, use of a selectable marker, such as URA3, HIS3, etc as the reporter gene

Cheng et al teach a method for identifying biologically significant peptide-DNA binding interactions and sequence-specific DNA binding peptides in vivo using combinatorial

oligonucleotide libraries, preferably in yeast (abstract). The method comprises providing host cells containing selectable markers, providing a recombinant vector containing a coding sequence encoding a protein that activates gene expression when in proximity to a target DNA sequence, the DNA sequence comprising a regulatory element, and the recombinant vector containing a selectable marker, inserting into the coding sequence in a plurality of recombinant vectors a random oligonucleotide so that the resulting vectors encode a plurality of different fusion proteins, each containing a protein that activates gene expression, and a peptide encoded by the random oligonucleotide, providing a reporter vector, the reporter vector comprising a reporter gene, the DNA regulatory element, and a selectable marker, co-transfecting the host cells with the DNA vectors and the reporter vectors, and then culturing the transfected host cells in a selective medium, so that only those host cells containing a vector DNA expressing a fusion protein that contains a peptide capable of sequence-specific binding to the target DNA sequence grow therein (column 2). Reporter genes for use in the method are taught as including HIS3, LEU2, TRP1, CAT, luciferase, and GFP (column 7). For HIS3, LEU2, and TRP1, the genome of the cells used lack a functional copy of the gene and the cells are maintained in a medium prepared without the

metabolite. Yeast, such as S. cerevisiae, are taught as host cells for the method (column 8). Cheng et al teach the method using yeast combinatorial libraries consisting of the Gal4 activation domain, a partial DNA binding domain that is unchanged (using two zinc fingers), and a synthetic oligo library which encode a test peptide for the rest of the DNA binding domain, which is changed (which corresponds to the target site) (column 14). Binding of the three finger positive control (which binds to the unaltered full DNA sequence) was compared to a two finger negative control polypeptide was compared, showing at least a 100-fold difference (column 16). This showed that binding of all three zinc fingers were required to specifically recognize the entire DNA sequence. Cheng et al teach that the previous way of using phage display combinatorial library techniques and affinity selection to identify peptide-nucleotide interactions fails to provide a method of identifying biologically significant peptide-DNA binding events, and the method taught by Cheng et al has the advantage of identifying biologically significant peptide-DNA binding interactions (column 1).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the piecewise mutagenesis of three zinc fingers in a polypeptide to each bind

to a corresponding altered part of the nucleotide sequence to which the polypeptide binds, testing the polypeptides that each contain one of the mutagenized zinc fingers for binding to the target nucleotide sequence by use of phagemid display/affinity, followed by constructing a nucleic acid that encodes all three mutagenized zinc fingers, taught by Barbas, by substituting the phagemid display/affinity selection with the in vivo expression method taught by Cheng et al because Cheng et al teach that it is within the ordinary skill in the art to use the in vivo expression method to identify peptide-DNA binding interactions, and Cheng et al specifically teach the use of this method to identify a peptide from a randomized library which binds to an altered target sequence in a polypeptide that also comprises two unaltered zinc fingers that bind the rest of the DNA sequence which is also not altered. This is the same type of mutagenesis taught by Barbas et al for modifying each of three separate zinc fingers to each separately bind to the altered part of an entire nucleotide sequence. Barbas also makes obvious this substitution because Barbas teaches that it is within the ordinary skill in the art to use the same type of in vivo expression method for identifying a modulating polypeptide.

It would have been obvious to make the substitution for the expected benefit of identifying the altered zinc finger peptides

which bind to the altered target sites in a biologically significant fashion and thus result in making a nucleic acid that encodes a polypeptide that has a biologically significant peptide-DNA binding interaction with the altered nucleotide sequence. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Regarding the use of three zinc finger domains for binding to the recruitment site, it would have been obvious to use one or more additional zinc fingers that bind to the unaltered nucleotide sequence because Barbas teaches that it is within the ordinary skill in the art to use the method taught by the reference to bind extended regions, using from 2 to 20 zinc fingers.

Regarding the use of amplifying a plurality of nucleic acids each of which encodes a test zinc finger domain using an oligonucleotide primer that anneals to a nucleic acid encoding a conserved domain boundary, it would have been obvious to do so because Barbas teaches the use of PCR to make mutagenized test zinc finger encoding DNA, with conserved boundaries in making the expression vectors.

Regarding the use of natural human zinc fingers as test zinc finger domains, it would have been obvious to do so because Barbas teaches that different zinc fingers can be used in the methods, including from proteins that are natural human proteins.

Regarding identifying a cell that expresses the reporter gene at least 10 fold higher than a given level, it would have been obvious to do so because the positive versus negative controls taught by Cheng et al showed at least a hundred fold difference and thus the method of Cheng et al would score as a positive result that level of difference of expression.

Claims 1-23, 32-33, 86, 88-93, and 95-98 are rejected under 35 U.S.C. 103(a) as being unpatentable over Barbas in view of Cheng et al as applied to claims 1-11, 13-22, 32-33, 86, 88-93, and 95-98 above, and further in view of Eisenberg et al (U.S. patent No. 6,453,242 B1, Applicant reference FB).

Barbas and Cheng et al are taught above and applied as before.

Barbas and Cheng et al do not specifically teach identifying a candidate zinc finger domain amino acid sequence in a sequence database, providing the candidate sequence, and

using the sequence to construct a hybrid nucleic acid for inclusion in the hybrid nucleic acids.

Eisenberg et al teach a method of designing a zinc finger protein comprising using a database and computer program to identify candidate zinc finger domains corresponding to first, second, and/or third fingers which bind a selected target sequence based upon a scoring system (columns 4-6). Rational criteria for design include application of substitution rules and computerized algorithms for processing information in a database storing information of existing zinc finger protein designs and binding data (column 7). A zinc finger protein binding to a novel sequence for which a precharacterized zinc finger protein does not exist can be made using this approach (column 17).

It would have been obvious to one of ordinary skill in the art at the time the invention was made to modify the method made from the combined teachings of Barbas and Cheng et al by using as a candidate zinc finger one of the zinc fingers identified in a database as binding a particular sequence as taught by Eisenberg et al because Barbas teaches that it is within the ordinary skill in the art to use any zinc finger in the method taught by the references and Eisenberg et al teach that it is within the ordinary skill in the art to use a zinc finger

protein from a database as the basis for the design of a zinc finger protein that binds to a novel sequence.

One would have been motivated to do so for the expected benefit of having a much larger and versatile starting point from which to design and test zinc finger proteins, a database which has many different zinc fingers, having many different binding specificities, which can be used as the basis for binding to an altered sequence. Based upon the teachings of the cited references, the high skill of one of ordinary skill in the art, and absent evidence to the contrary, there would have been a reasonable expectation of success to result in the claimed invention.

Conclusion

No claims are allowed.

Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS

of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action.

Certain papers related to this application may be submitted to Art Unit 1636 by facsimile transmission. The faxing of such papers must conform with the notices published in the Official Gazette, 1156 OG 61 (November 16, 1993) and 1157 OG 94 (December 28, 1993) (see 37 C.F.R. § 1.6(d)). The official fax telephone number for the Group is 571-273-8300. NOTE: If Applicant *does* submit a paper by fax, the original signed copy should be retained by applicant or applicant's representative. NO DUPLICATE COPIES SHOULD BE SUBMITTED so as to avoid the processing of duplicate papers in the Office.

Any inquiry of a general nature or relating to the status of this application or proceeding should be directed to (571) 272-0547.

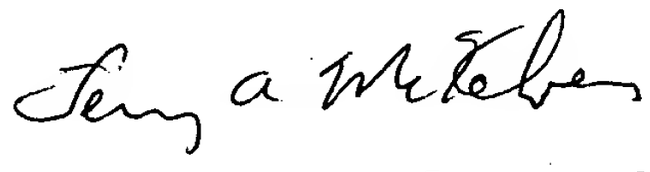
Patent applicants with problems or questions regarding electronic images that can be viewed in the Patent Application Information Retrieval system (PAIR) can now contact the USPTO's Patent Electronic Business Center (Patent EBC) for assistance. Representatives are available to answer your questions daily from 6 am to midnight (EST). The toll free number is (866) 217-9197. When calling please have your application serial or patent number, the type of document you are having an image problem with, the number of pages and the specific nature of the problem. The Patent Electronic Business Center will notify applicants of the resolution of the problem within 5-7 business days. Applicants can also check PAIR to confirm that the problem has been corrected. The USPTO's Patent Electronic Business Center is a complete service center supporting all patent business on the Internet. The USPTO's PAIR system provides Internet-based access to patent application status and history information. It also enables applicants to view the scanned images of their own application file folder(s) as well as general patent information available to the public.

For all other customer support, please call the USPTO Call Center (UCC) at 800-786-9199.

Any inquiry concerning rejections or objections in this communication or earlier communications from the examiner should

be directed to Terry A. McKelvey whose telephone number is (571) 272-0775. The examiner can normally be reached on Monday through Friday, except for Wednesdays, from about 7:30 AM to about 6:00 PM. A phone message left at this number will be responded to as soon as possible (i.e., shortly after the examiner returns to his office).

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Dr. Remy Yucel can be reached at (571) 272-0781.



Terry A. McKelvey, Ph.D.
Primary Examiner
Art Unit 1636

June 12, 2005